SOX10

Melanoma/Cancer Association

A melanoma patient with a positive clinical response to immunotherapy harbored a de novo immune response to epitopes of SOX10. These data, in combination with data showing that human melanomas and melanocyte cultures express elevated levels of SOX10, suggests SOX10 has potential as an immunotherapy target for melanoma (Khong and Rosenberg, 2002).

Analysis of SOX10 expression patterns and DNA binding activity during human melanoblast differentiation and in human melanoma cell lines found that **SOX10 levels were higher in melanoblasts and in melanoma cell lines relative to melanocytes**. In addition, culturing melanoblasts in melanocyte media conditions resulted in SOX10 downregulation, and culturing of melanocytes in melanoblast media conditions caused SOX10 upregulation. (Cook et al., 2005).

Melanoma gene expression profiling correlated two distinct transcriptional signatures with two phenotypes: 1) high proliferation with weak metastatic potential, or 2) weak proliferation with high metastatic potential. **The gene expression signature associated with high proliferation/weak metastatic potential contained elevated *SOX10* expression, in addition to increased expression of SOX10 downstream targets and intact activation of Wnt/beta-catenin signaling**. In contrast, the melanoma cell lines showing weak proliferation/high metastatic potential had increased TGFbeta signaling that resulted in inhibition of Wnt/beta-catenin signaling and decreased expression of *SOX10* (and SOX10 downstream targets) (Hoek et al., 2006).

Clear cell carcinoma (CCS), although a cancer derived from tendons and aponeuroses, displays melanogenic properties, including melanocyte differentiation markers, premelanosomes, and melanin production. CCS results from a chromosomal translocation that fuses Ewing's sarcoma-associated gene with activating transcription factor 1 (ATF1), which is a member of the CREB transcription factor family. This unique fusion protein induces *MITF* expression in CCS, and SOX10, which is also expressed in CCS, is required for the induction of *MITF* expression. MITF in turn is required for tumor cell growth and proliferation. The expression of SOX10 in CCS suggests that CCS is derived from a SOX10-expressing neural crest lineage. **The induction of MITF family members and presence of melanocyte histopathological markers in CCS, melanoma, pediatric renal cell carcinoma, and alveolar soft part sarcoma points to potential genetic/molecular relatedness of these clinically diverse cancers** (Davis et al., 2006).

In human and mouse gliomas, SOX10 is widely expressed. **RCAS virus expression studies showed that SOX10 is not an oncogene in gliomas**, as SOX1 expression alone is not sufficient to initiate tumor formation. However, SOX10 expression in combination with platelet-derived growth factor B increases glioma formation (Ferletta et al., 2007).

Expression analyses of a variety of tumor types and a large panel of melanomas indicates that **SOX10 expression may be a more sensitive marker for melanoma identification/diagnosis than S100 protein**, which also marks other forms of mesenchymal and epidermal tumors. SOX10 expression also was a more sensitive marker than S100 for clear cell sarcomas and peripheral nerve sheath tumors (Nonaka et.al.,2008).

SOX10, SOX9, BRN2 and Nestin co-expression were all demonstrated in melanoma. **Downregulation of SOX10 or SOX9 also resulted in downregulation of Nestin in melanoma cell lines, suggesting a requirement of these transcription factors for Nestin expression in melanoma**. In contrast, BRN2 expression was not required for Nestin activation, although expression levels of BRN2 and SOX10 protein correlate in melanomas (Flamminger et.al.,2009).

Using immunohistochemistry on nevi, primary melanoma, and advanced melanoma tissues, it was shown that

Nestin, SOX9 and SOX10 are co-expressed in melanoma. SOX10 specifically showed weak expression in 31% of nevi, variable expression in 43% of primary melanomas, and weak expression in 50% of metastatic melanomas. SOX10 exhibited subcellular localization to the perinuclear region and cytoplasm (Bakos et al., 2009).

Immunohistochemistry showed that SOX10 staining was 100% effective for the detection of metastatic melanoma in sentinel lymph nodes, thus suggesting that SOX10 as a single marker would be as effective as the commonly used trio of markers S100, HMB45, and Melan A (Blochin and Nonaka, 2009).

Using a genome-wide gain-of-function screen on the *MITF* promoter, TYRO3 was shown to regulate *MITF* transcription. This **TYRO3 regulation of *MITF* was shown to occur in melanoma cells, and appeared to act via SOX10; TYRO3 increased SOX10 nuclear expression, and in addition SOX10 inhibition removed the *MITF* activation by TYRO3** (Zhu et al., 2009a).

Mutations of *SOX10* were found in both primary and metastatic melanomas. Specifically, 6 mutations were found in 5 of 55 primary melanomas tested, and 3 mutations were found in 50 metastatic melanomas tested. Mutations in *MITF* were found as well in both primary and metastatic melanomas, strongly implicating the involvement of this pathway in melanoma progression. **Of note, the primary melanomas harboring *SOX10* and *MITF* mutations were either superficial spreading melanomas or mucosal, lentigo melanomas**. Proteins harboring the three metastatic melanoma *SOX10* mutations were shown to have reduced capabilities to synergistically activate transcription with *MITF*, while the 5 primary melanoma *SOX10* mutations showed abilities to activate transcription that were comparable to that of wild type *SOX10* (Cronin et al., 2009).

Coexpression of SOX10, PAX3, and the tyrosine kinase receptor MET was seen in melanoma cell lines and primary tumors. Although SOX10 alone did not activate transcription at a predicted SOX binding site in the *MET* promoter, **SOX10 was shown to act synergistically in two apparently independent pathways: 1, with PAX3 and 2, with MITF to activate expression of *MET*** (Mascarenhas et al., 2010).

Using immunohistochemistry, SOX10 staining was shown to be highly effective in marking in situ, invasive, and desmoplastic melanoma cells, yet did not show staining in fibroblasts or histiocytes of scars. SOX10 appeared to be a more effective melanoma marker than S100, which often shows staining in non-melanoma cell types (thus with false positive potential). In addition, SOX10 was also a more sensitive marker than MITF, HMB-45, or MLANA, which all show weaker staining in desmoplastic melanomas. The nuclear signal of SOX10 was also more readily distinguished than the cytoplasmic signals of other markers (Ramos-Herberth et al., 2010).

SOX10 protein expression was analyzed in normal melanocytes (n=16), benign nevi (n=6) and malignant melanomas (n=106 primary, 39 metastases). SOX10 staining intensity was strong in normal melanocytes and benign nevi, but **SOX10 staining intensity in malignant melanomas showed an inverse correlation between SOX10 intensity and T-stage. A trend towards direct correlation of SOX10 staining with overall survival and time to recurrence was observed. SOX10 protein showed an inverse correlation with expression of the proliferation marker Ki-67. SOX10 protein was expressed in all primary melanomas tested,** with 81% showing widespread expression. **Superficial spreading melanomas showed stronger staining than nodular malignant melanomas.** *SOX10* siRNA treatment of melanoma cell lines showed variable effects on proliferation and migration (Agnarsdottir et al., 2010).

By generating mice susceptible to melanoma (Nras(Q61K)::Ink4a$^{-/-}$) as well as deficient for Activating Transcription Factor 2 (*Atf2*) in melanocytes, it was shown that **lack of ATF2 function resulted in decreased melanoma susceptibility. Further analysis showed that ATF2 directly binds upstream of *Sox10*, regulating *Sox10* expression and that of downstream target genes, including *Mitf*. In normal mouse and human melanocytes as well as approximately 50% of melanomas, ATF2 inhibits *Sox10* expression**, while in a subset of melanomas, ATF2 activates *Sox10* expression. Further analyses showed that ATF2 heterodimerizes with JunB to inhibit *Sox10* expression, while ATF2 activation of *Sox10* expression in

melanoma occurs when ATF2 and JunB can no longer heterodimerize (Shah et al., 2010).

Melanoblasts isolated from human neonatal foreskin were cultured in two media conditions, one that allowed normal melanocyte formation, and one that induced melanocyte de-differentiation into melanoblast-related cells (MBrc). Comparative analysis of SOX10 mRNA expression in these two cultures showed that **SOX10 expression in MBrc cells was comparable to the SOX10 expression levels in melanoma cell lines (Mel Im and Mel Ju), and these SOX10 levels were higher than in normal melanocytes** (Bosserhoff et al, 2011).